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ORIGINAL

Prophylactic noninvasive ventilation after extubation in high-risk patients without hypercapnia

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Abstract

Purpose: The beneficial effects of prophylactic noninvasive ventilation (NIV) after extubation in patients without hypercapnia are uncertain. Our objective was to assess the effects of prophylactic NIV on reintubation among patients without hypercapnia at the time of extubation.

Methods: Post hoc analysis of two multicenter clinical trials including high-risk patients (i.e., patients older than 65 years or with underlying cardiac/respiratory disease). Our analysis focused on the 829 patients without hypercapnia ($PaCO_2 \leq 45$ mmHg), the day of extubation who received NIV alternating high-flow nasal cannula (HFNC) oxygen or HFNC alone after extubation. The primary outcome was the proportion of patients who required reintubation within seven days following extubation. We used G-computation to robustly estimate the marginal causal effect of treatment on the risk of reintubation.

Results: After extubation, 540 patients (65%) received NIV + HFNC while 289 (35%) received HFNC alone. The reintubation rate at day 7 was 11.8% [95% CI 9.4–14.8%] with NIV + HFNC versus 17.6% [95% CI 13.7–22.5%] with HFNC alone (difference, − 5.8% [95% CI − 11.2 to –0.8%]; $p = 0.021$). Using G-computation, NIV + HFNC was more effective than HFNC alone in reducing the risk of reintubation, with an estimated difference of − 5.6% [95% CI − 11.0 to − 0.5%]. Reintubation rates were also significantly lower with NIV + HFNC than with HFNC alone at 48 h, 72 h, and until ICU discharge.

Conclusion: For high-risk patients, but without hypercapnia on the day of extubation, the use of prophylactic NIV alternating with HFNC after extubation significantly decreases the risk of reintubation as compared to HFNC alone.

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Graphical Abstract:

PROPHYLACTIC NONINVASIVE VENTILATION AFTER EXTUBATION IN HIGH-RISK PATIENTS WITHOUT HYPERCAPNIA

Design

Post-hoc analysis of two multicenter randomized trials

Conclusion

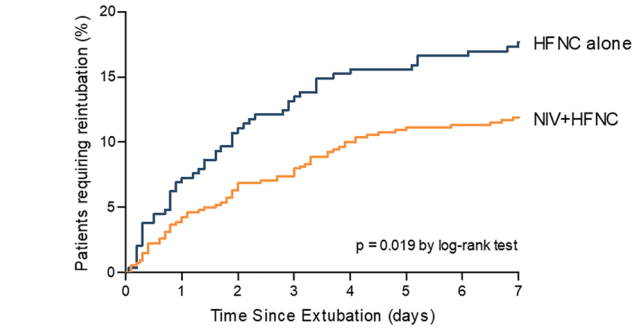
In high-risk patients without hypercapnia, prophylactic NIV + HFNC after extubation reduces reintubation compared with HFNC alone

Population

829 ICU patients at high risk of extubation failure but without hypercapnia ($PaCO_2 \leq 45$ mmHg) at extubation

Intervention

Prophylactic NIV alternating with HFNC vs HFNC alone after extubation



Number at risk.

HFNC alone	289	269	258	250	244	243	240	237
NIV+HFNC	540	519	505	498	484	473	471	467

	Reintubation by day 7
NIV + HFNC	11.8%
HFNC alone	17.6%
Absolute difference	−5.8% (p=0.021)
Adjusted analysis (G-computation)	Risk difference −5.6% (95% CI −11.0 to −0.5)

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ICM Intensive Care Medicine

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Introduction

In intensive care units (ICUs), while reintubation rates after planned extubation are around 10–15%, they may exceed 20% in patients at high risk of extubation failure [1, 2]. In these high-risk patients, several randomized controlled trials have shown that prophylactic non-invasive ventilation (NIV) applied immediately after extubation can prevent post-extubation respiratory failure and reintubation compared to standard oxygen and even compared to high-flow nasal cannula (HFNC) oxygen [3–8]. Therefore, the most recent international clinical practice guidelines recommend the use of NIV after extubation to prevent reintubation in patients considered at high risk of extubation failure [9, 10].

However, the presence or absence of hypercapnia at the time of extubation may be a major determinant of NIV success. In fact, the beneficial effects of NIV on alveolar ventilation and the relief of work of breathing are markedly more pronounced in hypercapnic patients [11], which makes NIV the standard treatment for acute hypercapnic respiratory failure [9, 10, 12, 13]. A major issue is that most clinical trials demonstrating

the benefits of prophylactic NIV after extubation have included a high proportion of hypercapnic patients [3, 5, 6, 8]. In these studies, approximately 30–40% of patients had hypercapnia at the time of extubation, which makes it unclear whether the beneficial effects of NIV extend to patients without hypercapnia. A previous clinical trial that included high-risk patients but excluded those with hypercapnia at the time of extubation found no difference in reintubation rates between NIV and HFNC [14].

Therefore, given the uncertain beneficial effects of NIV in non-hypercapnic patients, we aimed at assessing the effects of prophylactic NIV on outcomes among high-risk patients without hypercapnia at the time of extubation by pooling two large-scale clinical trials. We hypothesized that, compared to HFNC alone, prophylactic NIV alternating with HFNC may prevent reintubation, even in patients without hypercapnia.

Patients and methods

Study design and patients

We performed a post hoc analysis from two multicenter clinical trials on extubation [7, 15]. In the first study (641 patients included in 31 ICUs between 2017 and 2018), patients were randomized to receive either prophylactic NIV alternating with HFNC or HFNC alone during the first 48 h following extubation [7]. In the second study (969 patients included in 30 ICUs between 2020 and 2021), patients were randomized to undergo spontaneous-breathing trials with either pressure-support ventilation or with a T-piece to assess readiness for extubation. After extubation, prophylactic NIV alternating with HFNC was encouraged for at least 48 h [15]. Both studies had exactly the same inclusion criteria, *i.e.,* patients who had been extubated after at least 24 h of mechanical ventilation and following a successful spontaneous-breathing trial, and who were at high risk of extubation failure. Patients were considered to be at high risk of extubation failure if they were older than 65 years or had any underlying chronic cardiac or respiratory disease. Patients who had been admitted for traumatic brain injury, those who had pre-existing peripheral neuromuscular disease, and those who had a do-not-reintubate order at the time of inclusion were excluded.

Both original studies were approved by the central ethics committee and were registered at http://www.clinicaltrials.gov (NCT03121482 and NCT04227639). Written informed consent was obtained from all patients or next of kin before inclusion. In compliance with the national legislation regarding observational retrospective studies, this post hoc analysis was declared to European General Data Protection Regulation (MR004).

Inclusion criteria and treatment groups

The present study included all nonhypercapnic patients on the day of extubation ($PaCO_2 \leq 45$ mmHg under invasive mechanical ventilation) and who received either NIV alternating with HFNC (regardless of NIV duration) or HFNC alone as a prophylactic measure within the 48 h following extubation.

In both studies, the investigators were required to specify that NIV and HFNC were used as prophylactic measures. They also had to accurately report the total duration of NIV and HFNC within the 48 h following extubation and the timing of the onset of any potential post-extubation respiratory failure. Although NIV as rescue therapy for post-extubation respiratory failure was discouraged, all cases where therapeutic NIV was administered were systematically documented. To avoid bias and to compare only one additional intervention, i.e., the use of prophylactic NIV in the interventional group, patients who received standard oxygen instead of HFNC after extubation were excluded.

The recommended NIV protocol included initiating NIV as soon as possible after extubation, with a first session of at least 4 h. After that, the duration of NIV sessions was left to the discretion of the clinician, with a minimum duration of at least 12 h a day during the first 48 h following extubation. The recommended ventilator settings were a minimal pressure-support level of 5 cmH_2O targeting an expiratory tidal volume of 6–8 ml/kg of predicted body weight, and a positive end-expiratory pressure (PEEP) level between 5 and 10 cmH_2O and FiO_2 adjusted to obtain adequate oxygenation ($SpO_2 \geq 92\%$). The recommended settings for HFNC were a flow at 50 L/min, a temperature at 37 °C and FiO_2 adjusted to obtain adequate oxygenation ($SpO_2 \geq 92\%$).

Outcomes

The primary outcome was the proportion of patients who required reintubation within the seven days following extubation as in the original clinical trial comparing noninvasive respiratory supports after extubation [7]. Predetermined criteria for reintubation were exactly the same in both studies [7, 15].

Patients were immediately reintubated if one of the following criteria was fulfilled: (1) cardiac or respiratory arrest, (2) neurological failure defined as altered consciousness with a Glasgow coma scale below 12, (3) hemodynamic failure defined as the need for vasopressors and signs of hypoperfusion, or (4) severe respiratory failure defined by the presence of at least two among the following criteria: respiratory rate > 35 breaths per minute, clinical signs suggesting respiratory distress with increased accessory muscle activity, respiratory acidosis defined as pH < 7.25 units and $PaCO_2 > 45$ mmHg, and

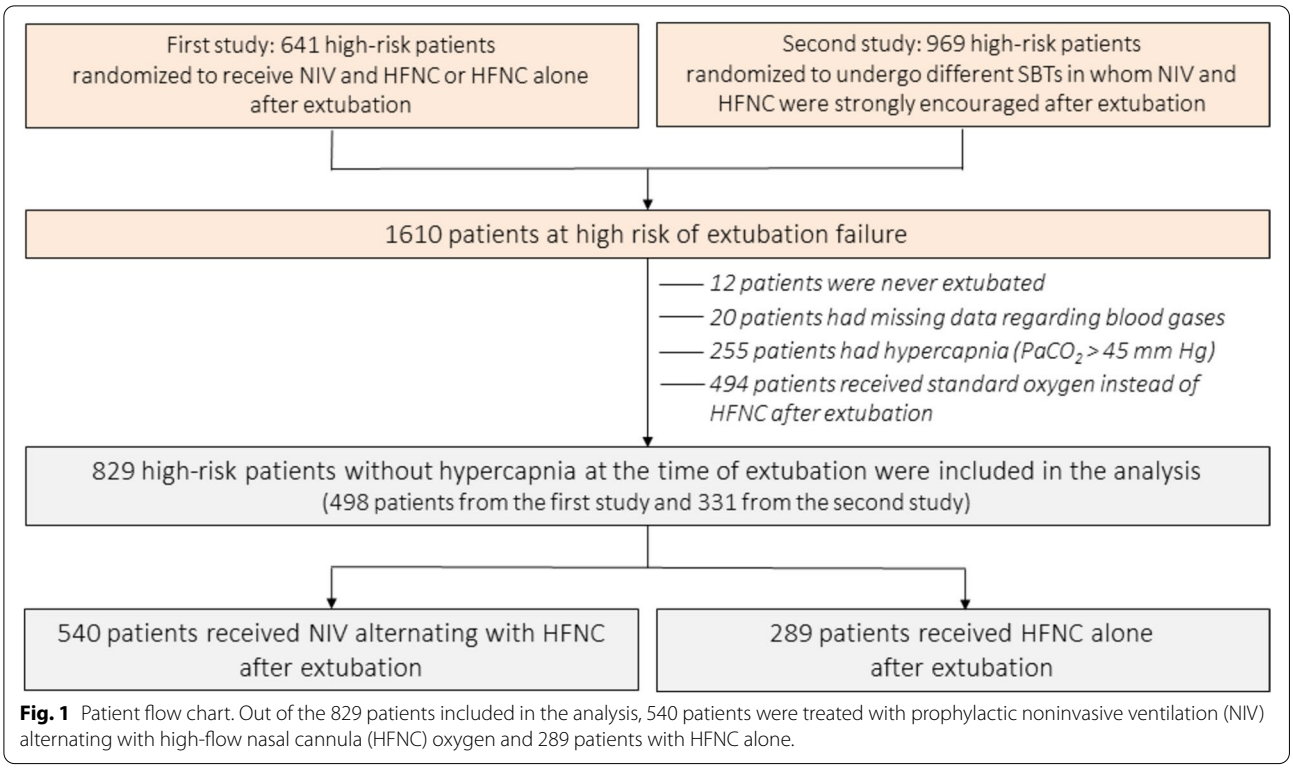

First study: 641 high-risk patients randomized to receive NIV and HFNC or HFNC alone after extubation
Second study: 969 high-risk patients randomized to undergo different SBTs in whom NIV and HFNC were strongly encouraged after extubation
1610 patients at high risk of extubation failure
12 patients were never extubated
20 patients had missing data regarding blood gases
255 patients had hypercapnia ($PaCO_2$ > 45 mm Hg)
494 patients received standard oxygen instead of HFNC after extubation
829 high-risk patients without hypercapnia at the time of extubation were included in the analysis (498 patients from the first study and 331 from the second study)
540 patients received NIV alternating with HFNC after extubation
289 patients received HFNC alone after extubation

Fig. 1 Patient flow chart. Out of the 829 patients included in the analysis, 540 patients were treated with prophylactic noninvasive ventilation (NIV) alternating with high-flow nasal cannula (HFNC) oxygen and 289 patients with HFNC alone.

hypoxemia defined as $PaO_2/FiO_2 < 100$ mmHg or a need for FiO_2 at least 80% to maintain $SpO_2 \geq 92\%$.

Secondary outcomes included post-extubation respiratory failure within the seven days following extubation, reintubation at 48h, 72h, and up until ICU discharge, length of stay and mortality in ICU, and mortality at day 28 and up to 60 days after extubation. Post-extubation respiratory failure was defined by the presence of at least two criteria among the following: respiratory rate > 25 breaths per minute, clinical signs suggesting respiratory distress, respiratory acidosis defined as pH < 7.35 units and $PaCO_2 > 45$ mmHg, and hypoxemia defined as $PaO_2/FiO_2 < 150$ mmHg or need for FiO_2 at least 50% to maintain $SpO_2 \geq 92\%$.

Statistical analysis

All analyses were performed by the study statisticians (L.C. and S.R.). Continuous variables were expressed as mean ± standard deviation or median [interquartile range, IQR 25th–75th percentiles], and qualitative variables as number and percentage. Characteristics at baseline and outcomes between patients treated with NIV alternating with HFNC (NIV + HFNC) and those treated with HFNC alone were compared by means of χ^2 test or Fisher's exact test for categorical variables, and Student's t test, Welch test, or Wilcoxon test for continuous variables depending on data distribution. The rates of reintubation within the seven days following extubation were compared between patients treated with NIV + HFNC and those treated with HFNC alone by means of the χ^2 test. Kaplan–Meier curves were plotted to assess the time from extubation to reintubation and were compared by means of the log-rank test at day 7. Characteristics of patients who required reintubation and those who were successfully extubated were compared using the same statistical tests.

Following this, we used G-computation within the counterfactual framework to estimate marginal causal effects as this approach allows for the direct estimation of risk differences while appropriately accounting for potential confounders and avoiding non-collapsibility issues that are inherent to odds ratios [16]. Missing data were addressed through multiple imputation by chained equations (MICE; five imputed datasets) [17].

We first used least absolute shrinkage and selection operator (LASSO) regression to identify the most relevant covariates for inclusion in our model. An optimal LASSO penalty (λ) was estimated in the full population and then applied to select covariates within each imputed dataset. We subsequently fitted a logistic regression model, adjusted for treatment assignment, clinically relevant confounders, and variables associated with reintubation, in order to predict the probability of reintubation

Table 1 Comparison between patients who received noninvasive ventilation (NIV) alternating with high-flow nasal cannula oxygen (HFNC) after extubation and those who received HFNC alone

Characteristics and treatments	NIV + HFNC ($n = 540$)	HFNC ($n = 289$)	p Value
Characteristics of the patients at admission			
Age, years	69 ± 9	70 ± 10	0.484
Male sex, *n* (%)	377 (70%)	193 (67%)	0.369
Body-mass index, kg/m^2	29 ± 7	28 ± 6	**0.021**
Obesity (BMI ≥ 30 kg/m^2), *n* (%)	210/532 (39%)	85/283 (30%)	**0.008**
SAPS II at admission, points	54 ± 19	55 ± 18	0.434
Underlying chronic cardiac disease, *n* (%)	269 (50%)	137 (47%)	0.508
Ischemic heart disease, *n* (%)	166 (31%)	72 (25%)	0.077
Atrial fibrillation, *n* (%)	84 (16%)	51 (18%)	0.437
Left ventricular dysfunction, *n* (%)	77 (14%)	44 (15%)	0.707
History of cardiogenic pulmonary edema, *n* (%)	32 (6%)	19 (7%)	0.711
Underlying chronic respiratory disease, *n* (%)	144 (27%)	55 (19%)	**0.014**
Chronic obstructive pulmonary disease, *n* (%)	100 (19%)	42 (15%)	0.147
Obesity-hypoventilation syndrome, *n* (%)	26 (5%)	10 (3%)	0.362
Chronic restrictive pulmonary disease, *n* (%)	27 (5%)	7 (2%)	0.075
Main reason for intubation, *n* (%)			0.419
Acute respiratory failure	288 (53%)	149 (52%)	–
Coma	80 (15%)	49 (17%)	–
Cardiac Arrest	60 (11%)	27 (9%)	–
Shock	44 (8%)	30 (10%)	–
Surgery	48 (9%)	29 (10%)	–
Other	20 (4%)	5 (2%)	–
Characteristics on the day of extubation			
Median duration of mechanical ventilation, days	6 [3–11]	6 [3–11]	0.408
Duration of mechanical ventilation ≥ 7 days, *n* (%)	253 (47%)	126 (44%)	0.370
SOFA score, points	4 ± 3	4 ± 3	0.563
Pressure-support ventilation mode, *n* (%)	447 (83%)	250 (87%)	0.162
Pressure-support level, cmH_2O	8.8 ± 3.1	9.4 ± 2.9	**0.021**
Positive end-expiratory pressure, cmH_2O	6.4 ± 1.7	5.8 ± 1.6	**< 0.001**
Tidal volume, ml/kg of predicted body weight	7.8 ± 2.2	7.7 ± 1.9	0.569
Respiratory rate, breaths/min	23 ± 6	23 ± 7	0.597
PaO_2/FiO_2, mmHg	269 ± 86	276 ± 91	0.275
$PaO_2/FiO_2 \leq 300$ mmHg , *n* (%)	371/538 (69%)	194/288 (67%)	0.638
pH, units	7.46 ± 0.05	7.46 ± 0.06	0.602
$PaCO_2$, mmHg	37 ± 5	37 ± 5	0.792
Type of SBT before extubation, *n* (%)			0.103
T – piece	299 (55%)	177 (61%)	
Pressure – support ventilation	241 (45%)	112 (39%)	
Hypercapnia at the end of the SBT, *n* (%)	27/275 (9.8%)	5/188 (2.7%)	**0.003**
Weaning difficulty, *n* (%)			0.744
Simple weaning (no more than 24h)	407 (75%)	217 (75%)	
Difficult weaning (more than 24h and less than 7d)	116 (22%)	60 (21%)	
Prolonged weaning (at least 7 days)	17 (3%)	12 (4%)	
Ineffective cough[a], *n* (%)	130/474 (27%)	59/269 (22%)	0.098
Abundant secretions[b], *n* (%)	150/486 (31%)	110/271 (41%)	**0.007**
Administration of steroids, *n* (%)	94 (17%)	38 (13%)	0.110
Noninvasive respiratory supports after extubation			
Prophylactic NIV after extubation, *n* (%)	540 (100%)	0 (0%)	**< 0.001**

Table 1 (continued)

Characteristics and treatments	NIV + HFNC ($n = 540$)	HFNC ($n = 289$)	p Value
Duration within the first 24h, hours	13 [8–15]	0 (0%)	**< 0.001**
Duration within the first 48h, hours	19 [11–26]	0 (0%)	**< 0.001**
HFNC after extubation, *n* (%)	540 (100%)	289 (100%)	–
Duration within the first 24h, hours	10 [8–14]	24 [24–24]	**< 0.001**
Duration within the first 48h, hours	22 [16–28]	48 [36–48]	**< 0.001**

Values are given in mean ± standard deviation or median [interquartile range, 25–75 percentiles] and number (%). In bold are indicated p values considered as statistically significant ($p < 0.05$)

NIV noninvasive ventilation, *HFNC* high-flow nasal cannula oxygen, *BMI* body-mass index, *SAPS* Simplified Acute Physiology Score, *SOFA* sequential organ failure assessment, *SBT* spontaneous-breathing trial

[a] Cough strength was scored using a semi-quantitative scale. It was graded 0 (absent), 1 (weak and ineffective), 2 (good and effective), or 3 (strong and very effective) and then defined as "ineffective" for a score of 0–1

[b] Likewise, sputum amount was graded from 0 to 3 according to the following definition: 0 (absence), 1 (low quantity), 2 (abundant), or 3 (very abundant) and then defined as "abundant" for a score of 2–3

Table 2 Comparison of outcomes between patients who received noninvasive ventilation (NIV) alternating with high-flow nasal cannula oxygen (HFNC) after extubation and those who received HFNC alone

Outcomes	NIV + HFNC ($n = 540$)	HFNC ($n = 289$)	Difference, % (95% CI)	p Value
Primary outcome				
Reintubation at day 7, *n* (%)				
Non-adjusted	64 (11.8%)	51 (17.6%)	− 5.8 (− 11.2 to − 0.8)	**0.021**
Adjusted difference using G-computation[a]			− 5.6 (− 11.0 to − 0.5)	–
Secondary outcomes				
Post-extubation respiratory failure, *n* (%)	102 (18.9%)	73 (25.3%)	− 6.4 (− 12.5 to − 0.5)	**0.032**
Reintubation at 48 h, *n* (%)	36 (6.7%)	32 (11.1%)	− 4.4 (− 8.9 to − 0.5)	**0.028**
Reintubation at 72 h, *n* (%)	40 (7.4%)	38 (13.1%)	− 5.7 (− 10.5 to − 1.5)	**0.007**
Reintubation in ICU, *n* (%)	68 (12.6%)	55 (19.0%)	− 6.4 (− 12.0 to − 1.3)	**0.013**
Length of stay in ICU, days	12 [7–20]	11 [7–20]	–	0.765
Mortality in ICU, *n* (%)	36 (6.7%)	19 (6.6%)	0.1 (− 3.8 to 3.4)	0.959
Mortality of reintubated patients in ICU, *n* (%)	25/68 (36.8%)	17/55 (30.9%)	5.9 (− 10.9 to 21.8)	0.496
Mortality at day 28, *n* (%)	53 (9.8%)	26 (9.0%)	0.8 (− 3.6 to 4.8)	0.702
Mortality at day 60, *n* (%)	79 (14.6%)	41 (14.2%)	0.4 (− 4.8 to 5.2)	0.863

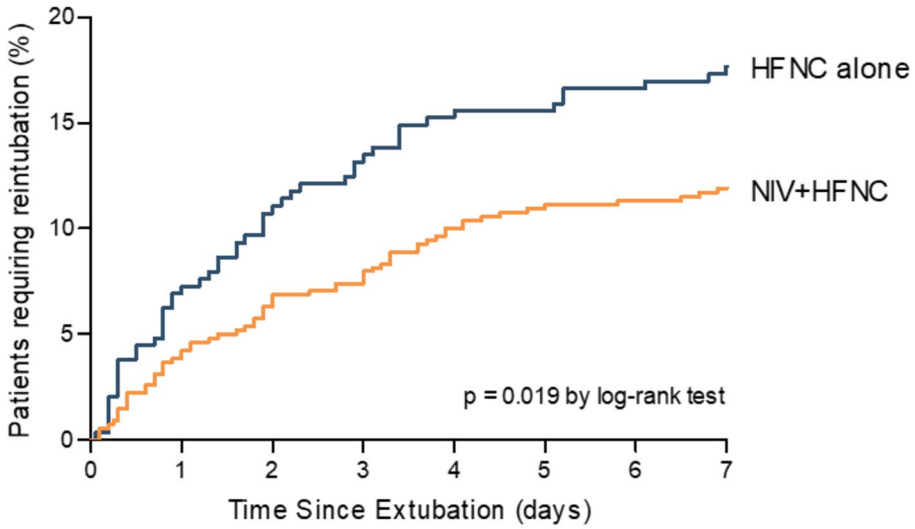
Values are given in median [interquartile range, 25 − 75 percentiles] and number (%)

In bold are indicated p values considered as statistically significant ($p < 0.05$)

ICU intensive care unit

[a] The logistic regression model used to predict the probability of reintubation using G-computation was adjusted on the following confounding variables: body − mass index, underlying chronic respiratory disease, prolonged duration of mechanical ventilation ≥ 7 days, severity SOFA score, PEEP level, respiratory rate, $PaCO_2$, cough strength, amount of secretions, and steroids before extubation. The missing data imputed for G-computation were the following: body-mass index ($n = 14$), positive end-expiratory pressure ($n = 1$), respiratory rate ($n = 11$), cough strength ($n = 86$), and abundant secretions ($n = 72$)

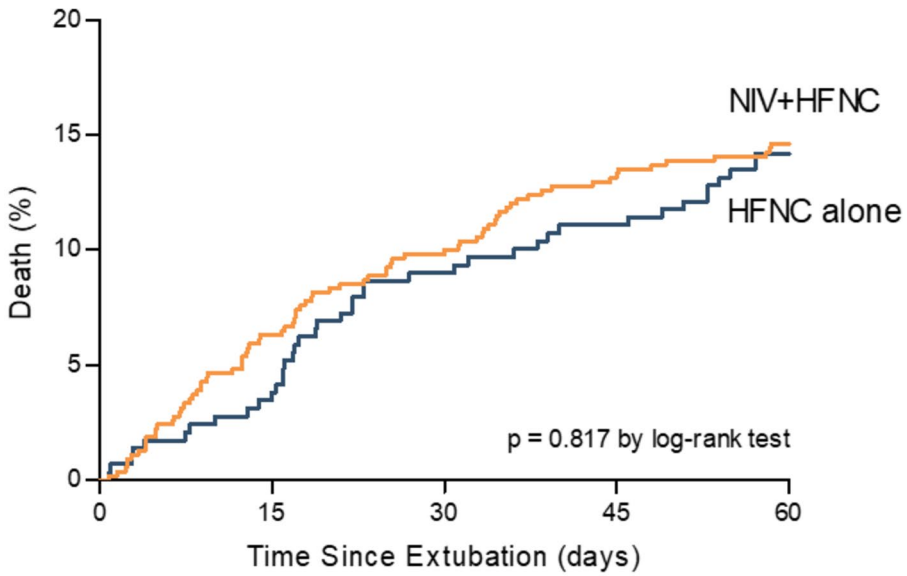
for each individual under both the treatment and the no-treatment scenarios. The average treatment effect was calculated as the mean difference between these predicted probabilities. Confidence intervals were estimated using bootstrap resampling (5 sets of 1000 replications each). Statistical analysis was conducted using R software version 4.0.4 (R Foundation for Statistical Computing; https://www.R-project.org) and G-computation using GitHub-chupverse/computation: an R package for causal inference using G-computation. A two-tailed p value of less than 0.05 was considered statistically significant.



Number at risk.

HFNC alone	289	269	258	250	244	243	240	237
NIV+HFNC	540	519	505	498	484	473	471	467

Fig. 2 Kaplan–Meier curves showing that the probability of reintubation during the seven days following extubation was significantly lower in patients who received noninvasive ventilation (NIV) and high-flow nasal cannula (HFNC) oxygen in orange than in those who received HFNC alone after extubation in blue ($p = 0.019$ using log-rank test).



Number at risk.

HFNC alone	289	278	263	257	248
NIV+HFNC	540	506	487	469	461

Fig. 3 Kaplan–Meier curves showing that the probability of death during the 60 days following extubation did not significantly differ between patients who received noninvasive ventilation (NIV) and high-flow nasal cannula (HFNC) oxygen in orange and those who received HFNC alone after extubation in blue ($p = 0.817$ using log-rank test).

Table 3 Timing, criteria and reasons for reintubation among patients reintubated within the 7 days following extubation

	NIV + HFNC ($n=64$)	HFNC ($n=51$)	p Value
Patients meeting pre-specified criteria for reintubation, *n* (%)	59 (92.2%)	45 (88.2%)	0.534
Time between extubation and reintubation, hours	47 (18–90s)	41 (17–82)	0.533
Criteria for reintubation[a], *n* (%)			
Severe respiratory failure	49 (76.6%)	36 (70.6%)	0.469
Neurological failure	21 (32.8%)	15 (29.4%)	0.696
Hemodynamic failure	7 (10.9%)	4 (7.8%)	0.752
Cardiac arrest	3 (4.7%)	6 (11.8%)	0.182
Reasons for reintubation[a], *n* (%)			
Copious secretions	26 (40.6%)	16 (31.4%)	0.306
Weakness of respiratory muscles	22 (34.4%)	11 (21.6%)	0.131
Ineffective cough	17 (26.6%)	9 (17.6%)	0.256
Atelectasis	9 (14.1%)	8 (15.7%)	0.807
Cardiogenic pulmonary edema	7 (10.9%)	7 (13.7%)	0.650
Upper airway obstruction	6 (9.4%)	6 (11.8%)	0.677
Alveolar hypoventilation	8 (12.5%)	2 (3.9%)	0.181
Septic shock	5 (7.8%)	4 (7.8%)	1.000
Need of procedure or surgery	3 (4.7%)	5 (9.8%)	0.463
Hypercapnic coma	2 (3.1%)	3 (5.9%)	0.654
Pleural effusion	2 (3.1%)	2 (3.9%)	1.000
Hemorrhagic shock	1 (1.6%)	3 (5.9%)	0.321
Cardiogenic shock	1 (1.6%)	1 (2.0%)	1.000

NIV non-invasive ventilation, *HFNC* high-flow nasal cannula oxygen

[a] A same patient may have several criteria/reasons for reintubation

Results

Out of the 1610 patients included in the two original clinical trials, 1578 patients underwent a blood gas analysis while under mechanical ventilation on the day of extubation (12 were never extubated and 20 had missing data regarding their $PaCO_2$ value at extubation). After excluding 255 patients (16%) with hypercapnia and 494 patients who received standard oxygen after extubation (352 who received NIV alternating with standard oxygen and 142 who received standard oxygen alone), 829 patients without hypercapnia were included in this analysis, of whom 540 (65%) received NIV+HFNC and 289 (35%) received HFNC alone after extubation (Fig. 1).

Patients who received NIV + HFNC were more likely to be obese and to have underlying chronic respiratory disease than those who received HFNC alone (Table 1). Although these patients were less likely to have abundant secretions before extubation, they more frequently developed hypercapnia by the end of the SBT. Among patients treated with NIV, 6.9% (37 out of 540 patients) did not tolerate more than 4 h of NIV.

Comparison of outcomes

The reintubation rate at day 7 was 11.8% (95% CI 9.4–14.8%) with NIV + HFNC vs. 17.6% (95% CI 13.7–22.5%) with HFNC alone (difference, − 5.8% [95% CI − 11.2 to − 0.8]; $p=0.021$ using the χ^2 test and $p=0.019$ using the log-rank test) (Table 2 and Fig. 2). Using G-computation to estimate the marginal causal effect of treatment, NIV + HFNC was more effective than HFNC alone in reducing the risk of reintubation, with an estimated difference in the rate of reintubation of − 5.6% [95% CI − 11.0 to − 0.5]. The logistic regression model using G-computation was adjusted in the following confounding variables: body mass index, underlying chronic respiratory disease, prolonged duration of mechanical ventilation ≥ 7 days, severity SOFA score, PEEP level, respiratory rate, $PaCO_2$, cough strength, amount of secretions, and steroids before extubation. The clinically relevant variables were selected based on comparisons between patients who required reintubation and those who were successfully extubated (Table S1).

Reintubation rates were also significantly lower with NIV + HFNC than with HFNC alone at 48 h, 72 h, and until ICU discharge. Mortality in the ICU, at days 28 and 60 was not significantly different between groups (Table 2 and Fig. 3).

A lower proportion of patients experienced post-extubation respiratory failure with NIV + HFNC than with HFNC alone. Median time from extubation to the

onset of post-extubation respiratory failure did not differ significantly between groups**:** 26 h [IQR, 7–62] with NIV + HFNC vs. 29 [IQR, 5–60] with HFNC alone ($p = 0.906$). NIV was used as rescue therapy for 23% of patients who experienced post-extubation respiratory failure after initially receiving HFNC alone (17 out of 73 patients). The time from extubation to reintubation, as well as the criteria and reasons for reintubation, did not differ significantly between the two groups (Table 3).

Hypercapnia at the end of the SBT

Out of the 829 patients, 463 (56%) underwent a blood gas analysis at the end of the SBT on the day of extubation. Among them, 32 patients (6.9%) developed hypercapnia ($PaCO_2 > 45$ mmHg) during the SBT. After excluding these 32 hypercapnic patients, the reintubation rate at day 7 was 12.1% (62 out of 513 patients) with NIV + HFNC versus 18.0% (51 out of 284 patients) with HFNC alone ($p = 0.023$). Among the 431 patients without hypercapnia at the end of the SBT, the reintubation rate was 12.5% (31 out of 248 patients) with NIV + HFNC versus 20.8% (38 out of 183 patients) with HFNC alone ($p = 0.021$). No significant interaction was found between hypercapnia at the end of the SBT and treatment group regarding the risk of reintubation ($p = 0.979$).

Discussion

This post hoc analysis from two large-scale clinical trials on extubation suggests that prophylactic NIV alternating with HFNC after extubation is more effective than HFNC alone at reducing the risk of reintubation in patients at high risk of extubation failure, even in the absence of hypercapnia on the day of extubation.

Treatments groups

We decided to compare prophylactic NIV + HFNC as intervention group versus HFNC alone as control group, and therefore, to exclude patients who received standard oxygen instead of HFNC. Several clinical trials have shown that HFNC is an alternative oxygenation strategy that may reduce the risk of reintubation as compared to standard oxygen [18, 19]. HFNC has even been found to be equivalent to NIV in preventing reintubation in nonhypercapnic patients considered at high risk of extubation failure in ICU [14]. Therefore, the use of standard oxygen alone would have been considered a suboptimal strategy for patients at high risk of extubation failure. After having decided to assess HFNC alone as control group, we decided to exclude patients who received NIV and standard oxygen in order to assess only addition of NIV to HFNC, *i.e.,* only one additional intervention.

Superiority of NIV over HFNC on the risk of reintubation

Two previous studies have shown that NIV was associated with a decreased risk of reintubation compared to HFNC [7, 8]. In the first study, which is part of the present post hoc analysis, 641 high-risk patients were randomized to receive NIV + HFNC or HFNC alone [7]. Randomization was stratified according to the $PaCO_2$ level in order to include the same number of hypercapnic patients in both groups, considering that NIV could be more effective in these patients. Although NIV + HFNC significantly reduced the risk of reintubation at day 7 compared to HFNC alone in the overall population, this reduction was only significant in patients with hypercapnia (17% of total population) [7]. These findings suggest that NIV may have a more pronounced effect on reintubation in patients with hypercapnia and that beneficial effects of NIV in nonhypercapnic patients should be confirmed in a larger sample size of patients. In the second study, continuous application of NIV within the first 24 h following extubation (without alternating with HFNC) significantly decreased the risk of reintubation at day 7 compared to HFNC [8]. This study included 181 patients considered at very high risk of extubation failure, and a high proportion of them had hypercapnia at the time of extubation (40% of total population). In contrast, a previous clinical trial performed by the same authors did not show any difference in reintubation rates between NIV and HFNC [14]. Although this trial also included patients at high risk of extubation failure, it excluded patients with hypercapnia at the time of extubation, which may explain the contradictory results, and suggest that beneficial effects of NIV on reintubation could be mainly driven by hypercapnic patients [8, 14]. A more recent clinical trial published by the same authors did not show a significant difference in reintubation rates albeit a trend among nonhypercapnic patients with obesity ($n = 144$) between those who received NIV and those who received HFNC [20]. These previous studies had smaller patient numbers than our current study, so they may not have had enough power to detect a significant difference in patients without hypercapnia. By combining our two clinical trials, we were able to include 829 nonhypercapnic patients receiving NIV + HFNC or HFNC alone, which is a markedly larger sample size. We observed a clinically relevant absolute difference of 5.8% in the reintubation rate, meaning that around 17 patients need to be treated to avoid one reintubation episode.

Limitations

One obvious limitation is that this is not a controlled trial comparing NIV + HFNC versus HFNC alone, and we cannot rule out remaining confounding factors, even after adjustment. Both trials included high-risk patients

fulfilling exactly the same definition. Moreover, we analyzed a large sample of patients and we performed relevant statistical analysis to mitigate causal inference and robustly assess the causal effects. The results remained significant even after adjustment using G-computation, which is likely the most appropriate method for controlling confounding bias [17]. Nevertheless, we performed multiple statistical comparisons on secondary outcomes, increasing the risk of type I error. Therefore, significant results should be interpreted with caution.

Another limitation is that $PaCO_2$ was assessed under mechanical ventilation on the day of extubation, and not at the end of the spontaneous-breathing trial, as in some previous studies [3, 4, 8]. While performing an arterial blood gas analysis at the end of the spontaneous-breathing trial is not always feasible, 56% of patients (463 of 829) underwent this procedure in our study, and only 6.9% of them (32 of 463) developed hypercapnia. Despite that, the risk of reintubation remained significantly lower with NIV, even after excluding patients with hypercapnia at the end of the SBT. Therefore, our findings indicate that measuring $PaCO_2$ under mechanical ventilation seems relevant, and above all allows for easier operational decisions without additional tests. However, we excluded patients who received standard oxygen instead of HFNC, which limits generalizability to the entire population of extubated patients.

We administered NIV for at least 12 h within the first 24 h following extubation, and believe that to ensure effectiveness, NIV should be administered at high doses. Although this approach is demanding, it aligns with most of the clinical trials demonstrating the beneficial effects of NIV in preventing post-extubation respiratory failure when high doses are used [3–8, 20]. In contrast, a more recent study found no significant reduction in reintubation when low doses of NIV were administered (5 h/day) [21].

Lastly, mortality did not significantly differ between groups. However, this is in accordance with most previous studies [5–8, 14, 20]. In our study, we observed a reduction of less than 6% in reintubation rates with NIV, while approximately one-third of reintubated patients died. These findings suggest that the expected reduction in mortality rates cannot exceed 1–2% in the overall population. In any case, reintubation is a significant patient-centered outcome representing a severe complication during an ICU stay and associated with increased medical resource utilization.

Conclusions

Compared to HFNC alone, prophylactic NIV alternating with HFNC after extubation was associated with a decreased risk of reintubation in high-risk patients without hypercapnia on the day of extubation in the ICU.

Supplementary Information

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Author contributions

Pr. Arnaud W. Thille had full access to all of the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis. AWT designed the study and wrote the manuscript. LC and SR performed statistical analysis. All authors contributed to drafting the work, revising it critically for important intellectual content, and approved the final version of the manuscript. All authors give their agreement to be accountable for all aspects of the work and ensure the accuracy and integrity of any part of the work.

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Data availability statement

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Declarations

Conflicts of interest
AWT reported receiving grants from the French ministry of Health, personal fees (payment for lectures and travel/accommodation expense coverage to attend scientific meetings) and nonfinancial support from Fisher and Paykel. Jean-Pierre Frat (JPF) has received personal fees for lecture and travel expense coverage to attend scientific meetings from Fisher & Paykel Healthcare and a grant for studies, personal fees as a member of a scientific board, and travel expense coverage to attend scientific meetings from SOS Oxygène.

Ethical approval
Both original studies were approved by the central ethics committee and were registered at http://www.clinicaltrials.gov (NCT03121482 and NCT04227639). Written informed consent was obtained from all patients or next of kin before inclusion. In compliance with the national legislation regarding observational retrospective studies, this post hoc analysis was declared to European General Data Protection Regulation (MR004).

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